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iVIEW

EDITOR'S PAGE

Capturing Maximal Coronary Vasodilation for Myocardial Perfusion Imaging

Is Timing Everything?

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Positron emission tomography (PET)-derived noninvasive quantification of hyperemic myocardial blood flow and flow reserve in absolute terms extends the scope of conventional single-photon emission computed tomography (SPECT) myocardial perfusion imaging from the detection of advanced and flow-limiting epicardial coronary artery disease to the early stages of atherosclerosis or microvascular dysfunction. Such regional and global absolute myocardial blood flow determinations by quantitative PET have identified coronary event risk incremental to that provided by severity of coronary artery stenosis.

The high spatial and contrast resolution of the photon attenuation-free images of PET along with the superior properties of PET myocardial blood flow tracers offers several advantages over SPECT. Unlike SPECT, in which an *extrinsic* collimator is used to limit the direction at which photons enter the detector, the coincidence detection with PET provides *intrinsic* collimation and improves the sensitivity of the camera. As a result, a number of clinical studies with myocardial perfusion PET have shown an improvement in sensitivity or specificity for the detection of coronary artery disease compared with SPECT, with overall diagnostic accuracy nearly 10% higher with PET than SPECT. Another important advantage of PET pertains to its ability to quantify regional myocardial blood flow in absolute (milliliters per gram per minute) rather than in relative (percentage radiotracer uptake) terms. Dynamic acquisition of PET radiotracer passing through the central circulatory system to its extraction and retention in the left ventricular myocardium in concert with tracer-kinetic modeling affords the assessment of regional myocardial blood flow of the left ventricle at rest and during vasodilator stress in absolute terms. However, accurate quantification of absolute myocardial blood flow with PET requires that the timing of the radiotracer injection be optimized to that of maximal coronary artery vasodilation.

Three U.S. Food and Drug Administration (FDA)-approved vasodilators are clinically available for myocardial perfusion studies: adenosine, dipyridamole, and regadenoson. Although the physiologic properties of these commonly used primary coronary vasodilator drugs are similar, there are noteworthy differences of each in terms of specific pharmacology, mechanism of action, administration, and timing and duration of maximal coronary artery vasodilation. Adenosine is a small endogenous compound produced by the endothelial cells that causes coronary vasodilation by activating the adenosine 2A (A_{2A}) receptor. However, because adenosine is an agonist of all 4 of its receptors (adenosine 1, A_{2A}, adenosine 2B, and adenosine 3), it may be associated with undesirable side effects, such as bronchospasm (adenosine 2B, adenosine 3) and conduction system (adenosine 1) problems. Dipyridamole is a nucleoside transport inhibitor and so increases interstitial fluid adenosine concentration by blocking its cellular uptake and subsequent degradation. Thus, dipyridamole serves as an indirect method for administering adenosine, and causing coronary vascular smooth muscle dilation. On average, the degree of myocardial hyperemia with dipyridamole has been found to be comparable to that of adenosine but with less consistent

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subject-to-subject myocardial hyperemic response than has been observed with adenosine. The more recently introduced selective A_{2A} receptor agonist regadenoson has considerably lower affinity for the other adenosine receptor subtypes, resulting in lesser frequency of side effects compared with adenosine. However, the clinical experience with regadenoson for assessing absolute myocardial blood flow with PET radiotracers has been lacking in published research.

In the present issue of *iJACC*, the results of a paired comparison of dipyridamole-induced myocardial hyperemia with that of regadenoson are reported using rubidium as the PET myocardial perfusion radiotracer (1). The investigators observed that hyperemic myocardial blood flow with regadenoson administered per the manufacturer's instruction (tracer injection ~10 to 20 s after a 5-ml flush of regadenoson [0.4 mg/5.0 ml]) was associated with only about 80% that of dipyridamole-induced hyperemic myocardial blood flow and flow reserve (142 μg/kg/min over 4 min, with rubidium injection 4 min after the completion of dipyridamole infusion). However, when rubidium injection was delayed to 55 s after regadenoson bolus injection, hyperemic myocardial blood flow increased to about 90% that of dipyridamole. These data suggest that accurate quantification of myocardial blood flow is critically dependent on the interplay between the vasodilator applied and the timing of the radiotracer injection in relation to the peak coronary vasodilation achieved by that particular vasodilator (2).

The more recent FDA approval of the A_{2A}-selective adenosine receptor agonist regadenoson was on the basis of a prospective, double-blind, randomized multicenter phase 3 trial comparing imaging results in patients undergoing standard gated adenosine SPECT myocardial perfusion imaging who were randomized in a 2:1 ratio to either regadenoson or a second adenosine SPECT study using single-photon emission radiotracers (thallium-201, technetium-99m sestamibi or tetrofosmin). PET and positron-emitting radiotracers (rubidium-82 or nitrogen-13 ammonia) were not studied, and absolute hyperemic myocardial blood flow or flow reserve was not quantified in the randomized trial. Upon receiving FDA approval, the manufacturer's recommendation for the optimal timing of radiotracer delivery after bolus injection of regadenoson was based on data from intracoronary flow sensors in animals as well as a small number of human subjects. Since attaining FDA approval, regadenoson has achieved widespread clinical application with both SPECT and PET technologies, with the assumption that all vasodilators and myocardial perfusion tracers are interchangeable (3), regardless of the instrumentation (SPECT or PET) or data analysis (qualitative vs. quantitative) applied (4). The realization that regadenoson underestimates the peak hyperemia achieved with dipyridamole vasodilator when studied with rubidium PET reported in the present issue of *iJACC* (1,2) underscores the importance of carrying out additional post-FDA approval studies, particularly if the use of the FDA-approved vasodilator is expanded beyond the original application in the phase 3 clinical trial.

Absolute myocardial blood flow assessment with pharmacologic vasodilator PET requires in-depth understanding of the timing and speed with which a vasodilator is administered in relation to peak coronary vasodilation and the extraction fraction of the radiotracer applied at higher flow rates. Before expanding the clinical application of an FDA-approved vasodilator with new technologies and/or radiotracers for quantitative assessment of myocardial blood flow, it would be prudent to undertake additional post-FDA approval clinical investigations.

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